BLUE CROSS OF NORTHEASTERN PA "BCNEPA" MEDICAL POLICY BULLETIN	**MANUAL:** MEDICAL POLICY
	REFERENCE NO.: MPO-083-0029
EFFECTIVE DATE July 1, 2014	**SUBJECT:** Genetic Testing for Alpha-1 Antitrypsin Deficiency

Blue Cross of Northeastern Pennsylvania ("BCNEPA") Medical Policy

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical policy and claims payment policy are applied. Policies are provided for informational purposes only and are developed to assist in administering plan benefits and do not constitute medical advice.

Treating providers are solely responsible for medical advice and treatment. Policies are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease.

Medical practices and information are constantly changing and BCNEPA may review and revise its medical policies periodically. Also, due to the rapid pace of changing technology and the advent of new medical procedures, BCNEPA may not have a policy to address every procedure.

In those cases, BCNEPA may review other sources of information including, but not limited to, current medical literature and other medical resources, such as Technology Evaluation Center Assessments (TEC) published by the Blue Cross Blue Shield Association. BCNEPA may also consult with health care providers possessing particular expertise in the services at issue.

DESCRIPTION:

Alpha-1 antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder that results in decreased production of the alpha-1 antitrypsin (AAT) protein or production of abnormal types of the protein that are functionally deficient. Individuals with AATD, especially smokers, have an increased risk of lung and liver disease. Tests are available to measure serum AAT levels and for AAT protein variant phenotyping. Genetic testing is also available to detect the most common mutations associated with AATD.

BENEFIT POLICY STATEMENT:

BCNEPA makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on product line, group or contract, therefore, Member benefits must be verified. In the event of a conflict between the Member's benefit plan document and topics addressed in Medical Policy Bulletins (i.e., specific contract exclusions), the Member's benefit plan document always supersedes the information in the Medical Policy Bulletins. BCNEPA determines medical necessity only if the benefit exists and no contract exclusions are applicable.

Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

BACKGROUND:

Description of disease:

AATD is an autosomal recessive genetic disorder that results in decreased production of the AAT protein, or production of abnormal types of the protein that are functionally deficient. Data from screening studies have found the prevalence of AATD in the United States to be between 1 in 2857 and 1 in 5097 individuals, respectively. (1)

AAT is an acute phase glycoprotein, primarily synthesized in the liver and secreted into the bloodstream. One of the primary functions of the AAT protein is to protect the lungs from damage by the enzyme elastase. Elastase, part of the normal response to injury and inflammation, breaks down proteins and can damage lung tissue if its action is not regulated by AAT. Individuals with AAT deficiency thus have an increased risk of lung disease.

Respiratory disease tends to be more severe and occur sooner (ie, between age 40 and 50) in individuals with AAT deficiency who smoke cigarettes and/or are exposed to occupational dust or fumes. In nonsmokers and individuals without environmental exposure, onset of respiratory disease occurs more commonly in the sixth decade. Childhood-onset lung disease is rare with AATD. AATD is also associated with an increased risk of liver disease, thought to occur due to aggregation of damaged AAT in the liver cells, where the protein is produced. The most common manifestation of liver disease in childhood is jaundice. Adults with AATD-associated liver disease generally present with cirrhosis and fibrosis. Panniculitis is a rare, but well-recognized complication of AAT deficiency. This dermatologic condition is characterized by inflammatory and necrotizing lesions of the skin and subcutaneous tissue. (2)

The primary interventions to prevent or treat symptoms in individuals with AATD involve behavioral change, especially avoiding or quitting cigarette smoking. Smoking is the most important risk factor for the development of emphysema in AATD in individuals who are homozygous for the most severe AAT mutations. (1) In addition, individuals with AATD are advised to avoid other substances that can irritate the lungs eg, cigarette smoke, dust and workplace chemicals, as well as substances such as alcohol that can cause liver damage. There are also general recommendations to exercise, avoid stress and have a nutritious diet. Furthermore, patients with AATD may be recommended to have earlier or more aggressive treatments for conditions such as asthma outbreaks or acute exacerbations of chronic obstructive pulmonary disease (COPD). One treatment option that is specific to AATD is alpha-1 antitrypsin augmentation. There are commercially available intravenous AAT augmentation products; patients generally receive injections of plasma every 3 to 4 weeks for life. Inhaled AAT augmentation therapy is under development. There is a lack of consensus about the efficacy of augmentation treatment.

Diagnostic testing for AAT:

Several types of tests are available for patients who are suspected of having AATD. A blood test is available that quantifies the total amount of AAT in the blood, detecting decreases in AAT protein levels, but not distinguishing among abnormal protein types. AAT is an acute phase reactant, and levels will be elevated in acute and chronic inflammatory conditions, infections and some cancers, which may cause levels to appear normal in individuals with mild to moderate AAT deficiency. In general, a serum concentration of AAT less than 15% to 20% of the normal value is highly suggestive of a homozygous AAT mutation. (3)

The alpha-1 phenotype test identifies the type of circulating AAT protein in the blood by isoelectric focusing of the various AAT protein types. Patterns of protein migration in an electric field are evaluated and compared with normal patterns to determine if and what type of abnormal AAT protein may be present.

Genetic testing is also available. Production of AAT is encoded by the *SERPINA1* gene, which is codominant (each gene copy is responsible for producing half of the AAT). Although there are more than 75 sequence variants of the *SERPINA1* gene (ie, 75 possible alleles), only several are common in North America. Approximately 95% of individuals have 2 copies of the normal M allele sequence (MM) and have mean serum concentrations of AAT ranging from 20 to 53 umol/L. The most common abnormal forms are the Z allele and the S allele. Individuals with 2 copies of the Z allele (ZZ) tend to be most severely affected, with mean serum concentrations of AAT of 2.5 to 7 umol/L and a high risk of COPD. Individuals with genotype SS and heterozygous individuals with genotype MZ have low risk of COPD and moderately lower levels of AAT. Individuals with rarer mutations of the *SERPINA1* gene or null alleles may not produce any AAT and are also at high risk. (4)

Genetic testing for AATD can be done with the alpha-1 genotype test. This test uses polymerase chain reaction analysis, or some other type of nucleic acid-based analysis, to identify abnormal alleles of AAT DNA. Currently, genotype tests are only designed to detect the most common mutations ie, the S and Z alleles.

A common approach to testing for AATD is to initially perform serum quantitation. If the AAT level is found to be low, a follow-up phenotype or genotype test is ordered. (5) Another approach, as exemplified by Mayo Clinic, is to perform serum protein quantification, followed by genotype testing in subjects with clinical suspicion of AATD. If these tests are discordant, phenotype testing is then performed. (6)

MEDICAL POLICY STATEMENT:

BCNEPA will provide coverage for genetic testing for alpha-1 antitrypsin deficiency when medically necessary.

Genetic testing for alpha-1 antitrypsin deficiency may be considered medically necessary when both of the following conditions are met:

1. Patient is suspected of having alpha-1 antitrypsin deficiency because of clinical factors and/or because the patient may be at high risk of having alpha-1 antitrypsin deficiency due to a first-degree relative with AAT deficiency (see Guidelines); AND

2. Patient has a serum alpha-1 antitrypsin level in the range of severe deficiency (see Guidelines).

Genetic testing for alpha-1 antitrypsin deficiency is considered investigational in all other situations.

GUIDELINES:

According to the 2003 joint statement on diagnosis and management of alpha-1 antitrypsin deficiency by the American Thoracic Society/European Respiratory Society, (1) the following features should prompt suspicion by physicians that their patient may be more likely to have AAT deficiency:

<u>Clinical factors</u>

- Early-onset emphysema (age of 45 years or less)
- Emphysema in the absence of a recognized risk factor (smoking, occupational dust exposure, etc.)
- Emphysema with prominent basilar hyperlucency
- Otherwise unexplained liver disease
- Necrotizing panniculitis

- Anti-proteinase 3-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis)
- Bronchiectasis without evident etiology

Family history

- A first-degree relative is defined as a parent, child, or sibling.

AAT deficiency occurs largely in Caucasians. For example, the prevalence in Sweden is approximately 1 in 1575, and the estimated prevalence in the United States is between 1 in 2857 and 1 in 5097. (1)
The following table shows the range of serum levels of AAT by common phenotypes according to the commercial standard milligram per deciliter (mg/dL) and the purified standard micromole (uM). A level of less than 11 □M is generally co
this cut-off may vary according to the specific test used (1,3):

	MM	MZ	SS	SZ	ZZ	Znull	Null-Null
μM	20-48	17-33	15-33	8-16	2.5-7	<2.5	0
mg/dL	150-350	90-210	100-200	75-120	20-45	<20	0

RATIONALE:

The literature on the analytic and clinical validity of genetic testing for AATD is limited. In addition, there are few RCTs evaluating the impact of alpha-1 antitrypsin deficiency (AATD) testing on patient outcomes. However, national guidelines recommend specific interventions for patients with emphysema and AATD, and alpha-1 antitrypsin (AAT) augmentation therapy is often prescribed for patients with AATD and chronic obstructive pulmonary disorder (COPD). The available evidence suggests that knowledge of AATD status may discourage nonsmokers from initiating smoking and may increase quit attempts among smokers, but it has not been shown to increase successful quitting. Evidence from small RCTs on AAT augmentation therapy are not definitive of a treatment benefit, but reports trend toward improvement in lung function. As a result, genetic testing for AATD may lead to improved outcomes by altering interventions for AATD and therefore may be considered medically necessary for individuals with suspected AATD or those at high risk for AATD due to personal or family history who have serum levels of AAT level in the range for homozygous disease.

Practice Guidelines and Position Statements

In 2012, the Canadian Thoracic Society published a clinical practice guideline on AAT deficiency testing and augmentation therapy. (16) The recommendations regarding targeted testing for AATD are:

- Targeted testing for AAT deficiency may be considered in those individuals with COPD who were either diagnosed before 65 years of age or who had less than a 20 pack-year history of smoking.
- Targeted testing for AAT deficiency is not recommended in individuals with bronchiectasis or asthma.

In 2003, the American Thoracic Society published recommendations on the diagnosis and management of individuals with AAT deficiency. (1)

Recommendations were classified as follows:

Type A: Genetic testing is recommended
Type B: Genetic testing should be discussed and could be accepted or declined
Type C: Genetic testing is not recommended i.e., should not be encouraged
Type D: Recommend against genetic testing i.e., should be discouraged

Type A recommendations for diagnostic testing in the following situations:

- Symptomatic adults with emphysema, COPD or asthma with airflow obstruction that is not completely reversible with aggressive treatment with bronchodilators;
- Individuals with unexplained liver disease
- Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (e.g. cigarette smoking, occupational exposure)
- Adults with necrotizing panniculitis
- Siblings of an individual with known alpha-1 antitrypsin (AAT) deficiency

Type B recommendations for diagnostic testing in the following situations:

- Adults with bronchiectasis without evidence etiology
- Adolescents with persistent airflow obstruction
- Asymptomatic individuals with persistent airflow obstruction and no risk factors
- Adults with C-ANCA positive (anti-proteinase 3-positive) vasculitis
- Individuals with a family history of COPD or liver disease not known to be attributed to AAT deficiency
- Distant relatives of an individual who is homozygous for AAT deficiency
- Offspring or parents of an individual with homozygous AAT deficiency
- Siblings, offspring, parents, or distant relatives of an individual who is heterozygous for AAT deficiency
- Individuals at high risk of having AAT deficiency-related diseases
- Individuals who are not at risk themselves of having AAT deficiency but who are partners of individuals who are homozygous or heterozygous for AAT deficiency

Type C recommendations for diagnostic testing in the following situations:

- Adults with asthma in whom airflow obstruction is completely reversible
- Predispositional testing
- Population screening of smokers with normal spirometry

Type D recommendations for diagnostic testing in the following situations:

- Predispositional fetal testing
- Population screening of either neonates, adolescents, or adults*

*Population screening is not recommended currently. However, a possible exception (type B recommendation) may apply in countries satisfying all 3 of the following conditions: 1) the prevalence of AAT deficiency is high (about 1/1,500, or more); 2) smoking is prevalent; and 3) adequate counseling services are available.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

DEFINITIONS:

N/A

CODING:

- **The identification of a code in this section does not denote coverage or separate reimbursement.**
- Covered procedure codes are dependent upon meeting criteria of the policy and appropriate diagnosis code.
- The following list of codes may not be all-inclusive, and are subject to change at any time.
- Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

PROCEDURE CODES

81332

SOURCES:

1. American Thoracic Society European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med 2003; 168(7):818-900.

2. Schlade-Bartusiak K, Cox DW. Alpha-1 antitripsin deficiency. In Pagon RA, Bird TD, Dolan CR et al. (eds.). Gene Reviews (internet). Seattle (WA): University of Washington. Available online at: http://www.ncbi.nlm.nih.gov/books/NBK1519/. Last accessed March, 2014.

3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Revised 2011. Available online at: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf. Last accessed March, 2014.

4. Kelly E, Greene CM, Carroll TP et al. Alpha-1 antitrypsin deficiency. Respir Med 2010; 104(6):763- 72.

5. Alpha-1 Foundation. Testing for Alpha-1. Available online at: http://alpha-1foundation.org/. Last accessed March, 2014.

6. Mayo Clinic. Test ID: A1ATR: Alpha-1-Antitrypsin Deficiency Profile. Available online at: http://www.mayomedicallaboratories.com/test-catalog/Overview/83050. Last accessed March, 2014.

7. Food and Drug Administration (FDA). 510(k) substantial equivalence determination decision summary (K063498). Available online at: http://www.accessdata.fda.gov/cdrh_docs/reviews/K063498.pdf. Last accessed March, 2014.

8. Ljujic M, Topic A, Divac A et al. Isoelectric focusing phenotyping and denaturing gradient gel electrophoresis genotyping: a comparison of two methods in detection of alpha-1-antitrypsin variants. Transl Res 2008; 151(5):255-9.

9. Lerman C, Gold K, Audrain J et al. Incorporating biomarkers of exposure and genetic susceptibility into smoking cessation treatment: effects on smoking-related cognitions, emotions, and behavior change. Health Psychol 1997; 16(1-Jan):87-99.

10. Audrain J, Boyd NR, Roth J et al. Genetic susceptibility testing in smoking-cessation treatment: one-year outcomes of a randomized trial. Addict Behav 1997; 22(6):741-51.

11. Carpenter MJ, Strange C, Jones Y et al. Does genetic testing result in behavioral health change? Changes in smoking behavior following testing for alpha-1 antitrypsin deficiency. Ann Behav Med 2007; 33(1):22-8.

12. Gøtzsche PC, Johansen HK. Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. Cochrane Database Syst Rev 2010; (7):CD007851.

13. Dirksen A, Dijkman JH, Madsen F et al. A randomized clinical trial of alpha1- antitrypsin augmentation therapy. Am J Respir Crit Care Med 1999; 160(5 pt 1):1468-72.

14. Dirksen A, Piitulainen E, Parr DG et al. Exploring the role of CT densitometry: a randomized study of augmentation therapy in alpha1-antitrypsin deficiency. Eur Respir J 2009; 33(6):1345-53.

15. Sponsored by Kameda Ltd. International Study Evaluating the Safety and Efficacy of Inhaled, Human, Alpha-1 Antitrypsin (AAT) in Alpha-1 Antitrypsin Deficient Patients With Emphysema (NCT01217671). Available online at: www.clinicaltrials.gov. Last accessed March, 2014.

16. Marciniuk DD, Hernandez P, Balter M et al. Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline. Canadian respiratory journal : journal of the Canadian Thoracic Society 2012; 19(2):109-16.

APPROVALS:

Approved by Vice President, Clinical Operations & Chief Medical Officer:

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HISTORY:

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Policy developed by: Medical Policy Department